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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,160	04/23/2001	Kristiina Ylihonko	1574/49849	9775

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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,160	YLIHONKO ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-11,16 and 18-22* is/are rejected.

7)☒ Claim(s) *4 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/23/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on June 12, 2003), Applicants filed an election and amendment received on September 22, 2003. Thus, Claims 1-22 are pending in the instant Office action.

Election

2. Applicant's election with traverse of Group I, Claims 1-4, 7-11, and 16-22 in a paper filed on September 22, 2003 is acknowledged. The traversal is on the ground(s) that all the claims share a unity of invention because of their common property of nogalamycin biosynthesis. This is not found persuasive because this feature is not presented as a claim limitation. The claims are limited to structural definitions alone, thus, to share unity of invention, the Groups must share the structure, which is not the case. Applicants also argue that once the cluster is searched, all the individual pieces have also been searched and, thus, no search burden can be cited to restrict the independent inventions. The Examiner disagrees because the entire cluster need not be searched to identify if the entire cluster is known in the art because if any one small piece is novel, the entire cluster must be novel. Moreover, the different functions of the entire cluster as opposed to its individual pieces render text searching burdensome as well.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-22 are pending in the instant application. Claims 5, 6, and 12-15 are withdrawn from further consideration as non-elected inventions. Claims 1-4, 7-11, and 16-22 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the International Application No. PCT/FI99/00870 filed on October 20, 1999 as requested in the declaration. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

The instant application is also granted the benefit of priority for foreign application 982295 filed in Finland on October 23, 1998 as requested in the declaration.

Information Disclosure Statement

4. The information disclosure statement filed on April 23, 2001 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with the Sequence Rules

5. The sequence listing filed in computer readable form and in paper copy on April 23, 2001 has been entered. Although the transmittal sheet on this date notes the enclosure of a statement of sameness under 37 C.F.R. § 1.821(f), no such statement is found in the file. Applicants must state, for the record, that the sequence listing filed in computer readable form and in paper copy on April 23, 2001 are the same.

Objections to the Specification

6. The specification is objected to for being unclear. In Figure 3, the abbreviation "NAME" must be described in the brief description of the drawings to be clear. Correction is required.

Objections to the Claims

7. Claims 1, 10, and 11 are objected to for typographical errors. The terms "anthracycline" and "antracyclinone" are misspelled. Correction is required.

8. Claim 4 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The plasmid pSY15c only contains a portion of the 10kb and 7kb fragments shown in Figure 2; this portion is the aL and aF genes inserted into said plasmid. To properly further limit from Claim 1, the plasmid must contain at least all the polynucleotide fragment required for the limitations of Claim 1. Because of this improper dependence, Claim 4 can no longer be treated on its merits as it is drawn to non-elected subject matter.

9. Claim 17 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The plasmid pSY15c only contains a portion of the 10kb and 7kb fragments shown in Figure 2; this portion is the aL and aF genes inserted into said plasmid. To properly further limit from Claim 2, the plasmid must contain at least all the polynucleotide fragment (or be 80% homologous to the fragment) required for the limitations of Claim 2. Because of this improper dependence, Claim 17 can no longer be treated on its merits as it is drawn to non-elected subject matter.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 3, and 7-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "ant[h]racycline biosynthetic pathway" is unclear as to its metes and bounds. Biosynthetic pathways are extensive and complicated as to just which genes are encompassed, particular in early stages of intermediate production. Either all the intermediates or all the genes/enzymes must be defined to clearly define a biosynthetic pathway.

The specification focuses on genes in Figure 2; some (not all) of these genes are assigned enzymatic steps on the pathway in Figure 3 converting D-glucose-1-PO_3 into nogalose and nogalamine and NAME into an aklavinone. These three sugars are combined with the aklavinone produce nogalamycin. Thus, this gene cluster, while being a portion of a gene cluster for the production of anthracyclines, actually appears to be only a gene cluster to produce particular portions of nogalamycin. In other words, SEQ ID NO:1 does not encompass "**the** gene cluster for **the** anthracycline biosynthetic pathway" (emphasis added). Clarification as to the functionality of the disclosed gene cluster is required; said clarification should extend into the claim language since one of skill in the art would interpret the phrase "the gene cluster for the anthracycline biosynthetic pathway" to encompass all the genes necessary to make anthracyclines.

11. Claims 2, 16, and 18-22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "80% homology" is unclear; no support in the specification can be found, except in the claims. Is this meant to be 80% identity over the full-length of SEQ ID NO:1? In the art, homology can apply to highly homologous portions of sequences. Thus, the metes and bounds of the term are unclear. Clarification is required.

12. Claims 7-11 and 18-22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "hybrid compounds" are totally unclear as to their metes and bounds. Is there some generic commonality of the compounds produced? Are they hybrids of some natural products? How is hybrid defined? Clarification is required. Claims 10-11 and 21-22 are included in this rejection because the formula compounds are not defined as the "hybrid compounds" produced.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 3 and 7-11 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. Claim 1 is drawn to a DNA fragment that is claimed solely by function and without any definite structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a DNA fragment that is a portion of a gene cluster for the anthracycline biosynthetic pathway is disclosed as SEQ ID NO:1. Said fragment can be found in the genome as two BglII-BglII fragments, one being about 10 kb and another being about 7 kb from the *S. nogalater* genome (see Figure 2). This limited structure of the gene cluster portion, namely size and restriction map, in no way correlates to the function required, only the structure that is SEQ ID NO:11 can do that. Without specific structure, the claim is drawn to any gene cluster for anthracycline biosynthesis that happens to be contained in fragments of the noted size and restriction map. Thus, the claims are drawn to a genus of DNA fragments, and one of skill

in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure.

14. Claims 2, 16, and 18-22 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 2 is drawn to DNA fragments with at least 80% homology to SEQ ID NO:1.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses a DNA fragment encoding polypeptides necessary to produce nogalamycin in a heterologous host cell; this DNA fragment of SEQ ID NO:1. Applicants have fully described the genus relating to said SEQ ID NOs with both sequence

identity limitations and functional limitations. However, the genus of the instant claims also contains DNA fragments within the sequence identity limitations, but having different function. Applicants have not fully described a genus that has sequence identity limitations in the absence of functional limitations.

15. Claims 2, 16, and 18-22 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for the DNA fragment that is SEQ ID NO:1, does not reasonably provide enablement for polynucleotides with such low sequence homology, such as the 80% claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The amount of experimentation required of one of skill in the art to use the claimed invention to the full extent of its scope is undue.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or

absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

Applicants present no guidance or working examples of the use of polynucleotides that have such low sequence identity with respect to SEQ ID NO:1. The nature of the invention is such that the DNA encodes functional proteins, those useful in the biosynthetic pathway of nogalamycin; and with such a great deviation from the known sequence, the predictability of functionality becomes extremely low. While the instant specification describes and enables means for identifying other anthracycline biosynthetic pathway genes using hybridization methods, etc., these methods do not enable one of skill in the art to make all, or a relevant portion of, the polynucleotides within the scope of the claims because the ability to find an anthracycline biosynthetic pathway gene, which is structurally related to SEQ ID NO:1, is not equivalent to the ability to make an anthracycline biosynthetic pathway gene as required by the statute (i.e., "make and use"). No description in the specification or the art provides particular residues whose encoding is important within the disclosed sequence so that its anthracycline-biosynthetic-pathway -nature is maintained. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

16. Claims 7, 8, 10, 11, 18, 19, 21, and 22 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of making nogalamycin-like in a *Streptomyces* host that naturally produces anthracyclines, does not

reasonably provide enablement for methods of increasing or producing in all *Streptomyces* hosts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The amount of experimentation required of one of skill in the art to use the claimed invention to the full extent of its scope is undue.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The instant specification teaches a gene cluster containing 17 genes described as encoding enzymes involved in nogalamycin biosynthesis; most activities of these encoded proteins are "deduced" according to homologous sequence in databases (although these homologous sequences are not disclosed) (see Table 1 on page 15 of the specification). Only 9 genes, those encompassed by pSY42, are used in functional assays in *S. galilaeus* H039 to produce formula I. Only snoaF and snoaL of the claimed DNA is transformed into S. lividans TK24 (as pSY15c) to produce formula II (nogalamycinone). Thus, no description of using the entire gene cluster in any *Streptomyces* host cell to make nogalamycin is taught. Moreover, from the figures, it is clear that SEQ ID NO:1 does not comprise all the genes necessary to make a complete anthracycline; said genes participate in the production of the sugars or the aklavinone. One of skill in the art would be unable to predict if SEQ ID NO:1 contains the entire gene cluster capable of producing anthracyclines in a heterologous host (that is, one that does not produce anthracyclines naturally). Thus, one of skill in the art would be unable to practice the claimed methods in all *Streptomyces* host cells. Claim 11 is included in the instant rejection because no

limitation of the derivation from *S. galilaeus* is in the claim, thus, the mutant used could be one that does not natively produce anthracyclines.

Art of Record

17. The following references are cited by the Examiner to complete the record concerning art in the field; none teach or render obvious the invention the pending claims.

a) Kunnari *et al*. Isolation and characterization of 8-demethoxy steffimycins and generation of 2,8-demethoxy steffimycins in *Streptomyces steffisburgensis* by the nogalamycin biosynthesis genes. J. Antibiotics (June, 1997) 50(6):496-501.

b) USPN 5,986,077 (Ylihonko *et al*.)

c) USPN 6,399,583 (Ylihonko *et al*.)

Conclusion

18. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

February 16, 2004